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Prospective study of the dietary inflammatory index and risk of breast cancer in postmenopausal women

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Abstract

Scope—Diet in relation to breast cancer etiology has been studied widely, but results have remained inconsistent. Various dietary components including fruits, vegetables, and meat have been implicated through their effects on inflammation. Using data from the Iowa Women's Health Study we examine prospectively the association between the dietary inflammatory index (DII) and breast cancer incidence.

Methods and results—DII scores were computed based on baseline dietary intake assessed by a validated 121-item food frequency questionnaire in a cohort of 34,700 women, aged 55-69 years at recruitment in 1986 and followed for incident breast cancer. During the 25-year follow-up period (1986-2011), 2910 incident breast cancer cases were identified. We used Cox proportional hazards regression to estimate multivariable hazard ratios (HR) and 95% confidence intervals (CI). We found positive associations between DII scores and breast cancer risk (HR for $DII_{tertiles}$: T_3vsT_1=1.11; 95% CI 1.00, 1.22), with stronger associations in obese women (HR for $DII_{continuous}$: 1.05 per unit increase in DII; 95%CI 1.02,1.12; HR for $DII_{tertiles}$: T_3vsT_1=1.35; 95%CI 1.10, 1.66, p-value for interaction=0.02).

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Author contribution: The authors' contributions were as follows: CB, AP and DJ designed and conducted the study, CB created the dataset for analyses, NS calculated DII and conducted all analyses and wrote the first draft of the manuscript, JRH, CB, AP and DJ provided suggestions and revised the manuscript. All authors approved the final version of the manuscript.

Conflict of Interest: None

Disclosures: Dr. James R. Hébert owns controlling interest in Connecting Health Innovations LLC (CHI), a company planning to license the right to his invention of the dietary inflammatory index (DII) from the University of South Carolina in order to develop computer and smart phone applications for patient counseling and dietary intervention in clinical settings. Dr. Nitin Shivappa is an employee of CHI. Dr. David Jacobs is a consultant to the California Walnut Commission.

Conclusion—A pro-inflammatory diet, as indicated by higher DII scores, appears to increase the risk of developing breast cancer, especially in obese postmenopausal women.

Introduction

According to the 2012 Global Cancer statistics, breast cancer is the most commonly diagnosed cancer and is the leading cause of cancer deaths in women worldwide, representing 25 per cent of all cancer cases and 15% of all cancer deaths [1]. In the US, it is the most common cancer in women, irrespective of race and ethnicity, and is the second most common cause of death from cancer [2]. There is strong evidence suggesting reproductive and hormonal factors [3] and a few strongly penetrant genes (e.g., BRCA1 and BRCA2) [4], as risk factors for breast cancer. The role of diet and inflammation in the etiology of breast cancer is unclear [5, 6]; however, some evidence suggests an etiologic role for diet, in particular the ability of foods to modulate inflammation in the etiology of the disease [7] with alcohol consumption being consistently shown to increase risk of breast cancer [8].

Typically, the body responds to any kind of tissue insult or injury by releasing inflammatory cytokines that result in acute inflammation, which leads to wound healing and successfully mounting an immune response to fight infections [9]. This response includes immune surveillance to identify and destroy early cancers [10]. By contrast, chronic inflammation is a persistent condition in which tissue destruction and repair occur simultaneously over a long period of time, which leads to chronic diseases such as obesity, diabetes and cancer [11, 12].

There is growing evidence, that specific dietary components influence both inflammation [13, 14] and breast cancer [15, 16]. Some food items such as fish and fruits exert an anti-inflammatory effect [17, 18], whereas dietary pattern rich in red meat increases inflammation [19]. Hormonal factors are important risk factors related to breast cancer[20] and there is evidence showing inflammatory cytokines which regulate inflammation in breast carcinogenesis to modify this association [21].

The Dietary Inflammatory Index (DII) [22], is a tool developed to measure the inflammatory potential of diet and it has been used in diverse populations to predict levels of inflammatory markers including C-reactive protein [23] and interleukin-6 [24]. The DII also is associated with various other cancers including colorectal [25-27], pancreatic [28], and prostate [29]. Thus far, the association between DII and breast cancer incidence has been inconsistent. In one case-control study in Germany and one cohort study in the US, no association was observed [6, 30], while in a prospective study conducted in Sweden and a case-control study in Italy, increasing DII score was found to be associated with breast cancer [5, 31]. To test the dietary inflammation-breast cancer hypothesis, we examined the association between the DII and breast cancer incidence in a large prospective cohort of postmenopausal women from the Iowa Women's Health study (IWHS). Our working hypothesis is that a higher DII score (indicating a pro-inflammatory diet) is associated with an increased risk of incident breast cancer.

Subjects and Methods

Study cohort

Design and Participants—Full details regarding the IWHS design have been published elsewhere [32]. In brief, 41,836 women ages 55–69 years, respondents from among over 99,000 randomly selected Iowa Driver's License holders were enrolled in 1986 (42% response rate). Incident cancer cases and deaths were identified through annual linkage with the State Health Registry of Iowa (a Surveillance, Epidemiology and End Results program member) and the National Death Index. Emigration from Iowa was less than 1% annually, resulting in complete follow-up [33]. Women with self-reported history of cancer prior to baseline, except non-melanoma skin cancer (n=3,830); or extreme energy intake (< 600 kcal or ≥ 5000 kcal per day) or incomplete dietary data (≥30 items blank) on the food frequency questionnaire (FFQ) (n=3,096) were excluded from the present study, yielding an analytic sample consisting of 35,216 study participants (exclusions were not mutually exclusive). After further exclusion for missing covariates, data from 33,817 women were included in the analysis. Dietary intake data were collected using the FFQ at baseline. This 121-item FFQ was adapted from the 126-item instrument developed by Willett and colleagues [34]. Questions related to supplements were part of this FFQ and were incorporated into the DII calculation. FFQ-derived dietary data were used to calculate DII scores for all participants. The University of Minnesota Institutional Review Board approved this study, and all participants gave consent.

Dietary Inflammatory Index (DII)

The entire process of developing the DII is described elsewhere [22]. FFQ-derived dietary data were used to calculate DII scores for all participants. To calculate the DII for the participants of this study, FFQ-derived dietary data were first linked to the previously described regionally representative world database that provided estimates of the mean and standard deviation for each parameter [22]. These then became the multipliers to express an individual's exposure relative to the "standard global mean" as a z-score. This score was computed by subtracting the "standard global mean" from the amount reported and dividing this value by the "global standard deviation" of the world population as represented by the 11 data sets used for comparative purposes. To minimize the effect of "right skewing", this value was then converted to a centered percentile score.

For each individual food parameter, this score was then multiplied by the respective food parameter effect score, derived from the literature review, in order to obtain a food parameter-specific DII score [22]. All of the food parameter-specific DII scores were then summed to create the overall DII score for every participant in the study, DII= b1*n1+b2*n2.....b45*n45, where b refers to the literature-derived inflammatory effects score for each of the evaluable food parameters and n refers to the food parameter-specific centered percentiles, which in the present case were derived from the IWHS dietary data. A description of validation work, including both dietary recalls and a structured questionnaire similar to an FFQ, also is available [23].

For the current study, data on 29 of the 45 food parameters could be derived from the IWHS FFQ and were thus used for DII calculation (the remaining 16 food parameters were ignored). Of these, energy, carbohydrates, cholesterol, proteins, total fat, vitamin B12, saturated fatty acids, and trans fat are pro-inflammatory. Alcohol, fiber, monounsaturated fatty acids, polyunsaturated fatty acids, omega 3 fatty acids, omega 6 fatty acids, niacin, thiamin, riboflavin, vitamin B6, iron, magnesium, zinc, selenium, vitamin A, vitamin C, vitamin D, vitamin E, folic acid, beta carotene and garlic are anti-inflammatory.

Follow-up

The cohort was followed from 1986 until December 31st, 2011. Person-years of exposure time were accumulated from baseline until first primary breast cancer diagnosis, move from Iowa, death, or administrative censoring on 12/31/2011. Our outcome was defined as a diagnosis of newly incident breast cancer (International Classification of Diseases, ICD-O-3 codes C50.0-C50.9). A total of 2910 incident breast cancer cases were identified after exclusion of observations with missing covariates.

Statistical analyses

Distribution of characteristics across tertiles of DII scores was tested using ANOVA for continuous variables (age at baseline, age at menarche and age at menopause) and Chi-square for categorical variables: normal weight, overweight and obesity based on body mass index [BMI = weight (kg)/weight (m)^2], education, smoking, number of live births, hormone replacement therapy (HRT) and oral contraceptive (OC) use and history of hysterectomy. Hazard ratios and 95% confidence intervals (HR; 95% CI) were estimated using Cox proportional hazards regression models, adjusting only for age and energy in the crude model and additionally adjusting for BMI, smoking status, education, HRT use, oral contraceptive use, number of live births, education, age at menarche, age at menopause and history of hysterectomy in the fully adjusted model. Covariates were chosen *a priori* as they were previously shown to be associated with breast cancer. The assumption of proportional hazards was tested by adding to the model an interaction term between follow-up time and DII; there was no evidence that this assumption was violated. The DII was analyzed both as a continuous variable, (each point corresponded to a 1-unit increment in DII, which is a 0.5 standard deviation increase), and by tertiles; We categorized DII into tertiles to allow for examination of a non-linear relationship between DII and breast cancer incidence. In the analysis of categorized DII, a linear test for trend was conducted by including the median value for each DII tertile as a continuous term in the regression model. Test for interaction was carried out by including the interaction term in the model and via stratification by BMI (<25, 25-29.9, ≥30 kg/m^2). Statistical tests were performed using SAS® 9.4 (SAS Institute Inc., Cary, NC). All statistical tests were conducted using a two-sided 5% level of significance.

Results

The mean DII score and the corresponding standard deviation (SD) in this study is −0.87 ± 2.02. Baseline characteristics of women across tertiles of DII are provided in Table 1. Women in the third tertile (representing a more pro-inflammatory diet) were slightly though

significantly more likely to be obese, to have lower educational attainment, be current smokers, to have a higher number of live births, and be less likely to have ever used hormone therapy and to have had a hysterectomy.

Table 2 shows age- and energy-adjusted and multivariable-adjusted HRs of breast cancer according to the DII presented as tertiles and as continuous. In the multivariable-adjusted model, women in the highest tertile of DII (a more pro-inflammatory diet) had an 11% higher risk of developing breast cancer compared to women in the lowest tertile (P_{trend}=0.06); no significant association was observed with continuous DII (Table 2). Table 3 shows multivariable HRs of breast cancer in strata of BMI categories. Stronger associations were observed between DII and breast cancer risk among obese women (BMI >30 kg/m^2) with a 22% increased risk (95% CI =1.01, 1.48) and a 35% increased risk (95% CI = 1.10, 1.66) of breast cancer among women in the second and third tertiles, respectively (P_{trend}=0.01). For every 1-unit increment in DII (corresponding to a 0.5 standard deviation increase), there was a 5% increased risk of breast cancer among obese women compared to normal weight women (95% CI=1.01, 1.10; interaction *p* values were 0.02 for DII continuous).

Discussion

In this large population-based prospective study of postmenopausal women from Iowa, we found evidence of a positive association between increasing DII score and incident breast cancer in obese women. Results in normal-weight and over-weight women, though suggestive of an effect, were not statistically significant. In general, these results support our hypothesis that women consuming a more pro-inflammatory diet are at increased risk of breast cancer. Previously, the DII has predicted colorectal cancer incidence and mortality in the IWHS [25, 35]. Multivariable analysis, revealed positive associations between higher DII and colorectal cancer risk [HR for DIIquintiles: Q5 vs. Q1 = 1.20; 95% CI, 1.01-1.43] [25], all-cause mortality (HRQ4vsQ1 1.07; 95 % CI 1.01-1.13), digestive cancer mortality (HRQ4vsQ1 1.19; 95 % CI 1.00-1.43), CVD mortality (HRQ4vsQ1 1.09; 95 % CI 1.01-1.18), coronary heart disease (CHD) mortality (HRQ4vsQ1 1.17; 95 % CI 1.05-1.30) and chronic obstructive pulmonary disease (COPD) mortality (HRQ4vsQ1 1.43; 95 % CI 1.18-1.75) [35].

Previous studies on diet and breast cancer have shown mixed results. A recent meta-analyses of 24 prospective cohort studies suggested that dietary total fat and fatty acids might not be associated with increased risk of breast cancer [36]. In another meta-analyses of data from 21 prospective cohort studies, higher consumption of dietary marine n-3 polyunsaturated fatty acids were associated with a lower risk of breast cancer [37]. Some studies have shown that Mediterranean diet and diets composed largely of vegetables, fruit, fish, and soy are associated with a decreased risk of breast cancer [38]. Previous reports on diet and breast cancer in the IWHS showed a protective role of vitamin D intake of >800 IU/day [39], and no association with vitamins A, C and E [40].

We observed a stronger association between DII and breast cancer among obese women. Obesity is a state of chronic low-grade inflammation and has been shown to be positively

associated with postmenopausal breast cancer, and combined with poor diet (higher DII scores) may accentuate the risk of breast cancer among postmenopausal women [41].

Thus far, there have been two previous studies conducted to explore the association between DII and breast cancer. In a case-control study conducted in Germany, no significant association was observed between the DII score and postmenopausal breast cancer risk (adjusted OR Q5 vs Q1: 1.01, 95% CI: 0.86-1.17) [6]. In the Women's Health Initiative, DII was not associated with incidence of overall breast cancer (HRQ5vsQ1, 0.99; 95% CI, 0.91-1.07) whereas increasing DII was associated with a higher risk of death from breast cancer (HRQ5vsQ1, 1.33; 95% CI, 1.01-1.76) [30]. However, in a prospective study conducted in Sweden, a positive association was observed between DII and breast cancer (HR $DII_{quartile\ 4\ vs\ 1}$=1.18; 95% CI: 1.00, 1.39), which was the same in postmenopausal women (HR $DII_{quartile\ 4\ vs\ 1}$=1.22; 95% CI: 1.01, 1.46) [5], a positive association was also seen in a recent report from an Italian case-control study (OR $DII_{quartile\ 4\ vs\ 1}$=1.75; 95% CI: 1.39, 2.21) [31].

Results of breast cancer-DII analyses are not as consistent and strongly positive as those observed with colorectal cancer [25-27], which is known to be more strongly associated with chronic inflammation [42, 43]. Another explanation for this discrepancy includes the role of other risk factors, such as reproductive and hormonal factors [3], that may play a stronger role than diet and inflammation in breast cancer and cannot be fully accounted for. Thus, the modest results obtained in this study shows risk due to just the inflammatory potential of diet may be relatively weaker than for other cancers. A positive association of the DII with breast cancer in the IWHS study might arise through the effect of a pro-inflammatory diet on levels of inflammatory cytokines, specifically IL-6, i.e. through increasing systemic inflammation [44]. Consumption of a pro-inflammatory diet rich in food items such as meat and butter increases systemic inflammation by increasing levels of IL-6 [45]. IL-6 is involved in the Stat3 pathway, which results in the induction of carboxylic acid (COOH) terminal and increased expression of fascin, both of which play an important role in breast cancer cell migration and invasion [45].

Strengths of the present study include its population-based design, large sample size, large number of cases, prospective data collection with extended, nearly complete follow-up, near-complete case ascertainment and adjustment for multiple potential confounding factors. Disease-related information bias was unlikely because of the prospective design to the study and adult dietary patterns appear to remain relatively stable over time [46, 47]. Additionally, there was no specific dietary intervention applied to participants during the course of the study. Still, a change in dietary pattern since baseline could produce a different effect of diet. Another limitation could be the non-availability of the remaining 16 food parameters that could contribute to calculating the DII. Missing food parameters such as turmeric, thyme, and saffron, are likely consumed in small amounts, infrequently or not consumed at all in this population; hence, their absence may have had little impact on the scoring. However, missing information on food parameters such as garlic and onion that are more likely to be consumed in this population may have played a role in this association. It is also important to note that IWHS has a predominantly non-Hispanic White population (99.2% of the study population), so the results may not be generalizable to other ethnic and racial groups.

In conclusion, women who consumed a more pro-inflammatory diet were at increased risk of breast cancer compared to women who consumed an anti-inflammatory diet. The highest, and only statistically significant, risk was observed among obese women. Our results provide evidence for the benefits of a diet high in food items that decrease inflammation and low in food items that increase inflammation.

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Table 1

Prevalence of characteristics at baseline across tertiles of dietary inflammatory index (DII) in the Iowa Women's Health Study, 1986-2011.

Characteristics[a] (mean (SD) or %)	DII Tertiles[c]		
	< −2.08	−2.09 to −0.05	> −0.05
Age (y) [b]	61.9 (4.2)	61.5 (4.2)	61.3 (4.1)
Age at menarche [b]	12.8 (1.5)	12.8 (1.4)	12.9 (1.4)
Age at menopause [b]	47.9 (6.4)	47.7 (6.3)	47.3 (6.4)
BMI categories (%) (kg/m^2)[b]			
≤24.9	4563 (41.6)	4281 (39.2)	4200 (38.9)
25-30	4041 (37.1)	4065 (37.4)	3929 (36.2)
≥30	2308 (21.3)	2545 (23.4)	2691 (24.9)
Education (%)[b]			
Less than high school	1655 (15.3)	1920 (17.7)	2167 (20.2)
High school	4165 (38.4)	4510 (41.6)	5050 (46.6)
More than high school	5092 (46.3)	4461 (40.7)	3603 (33.2)
Smoking (%)[b]			
Never	7575 (70.0)	7182 (66.8)	6557 (61.3)
Former	2174 (19.5)	2088 (18.7)	2119 (19.2)
Current	1163 (10.5)	1621 (14.5)	2144 (19.5)
Number of Livebirths [b]			
0	999 (9.2)	948 (8.8)	971 (9.1)
1-2	3530 (32.4)	3428 (31.5)	3506 (32.2)
3-4	4434 (40.6)	4373 (39.9)	4216 (39.0)
>4	1949 (17.8)	2142 (19.8)	2127 (19.7)
Hormone therapy use (yes) (%)[b]	4646 (42.6)	4212 (38.5)	3819 (35.2)
Oral contraceptive use (yes, %)	2134 (19.4)	2123 (19.2)	2099 (19.1)
History of hysterectomy(yes, %) [b]	3739 (34.5)	3450 (31.9)	3423 (31.8)

[a] All variables are at baseline (1986)

[b] Characteristics showing significant trend across tertiles.

[c] First tertile represents a more anti-inflammatory diet; third tertile represents a more pro-inflammatory diet.

Table 2

Hazard ratios (HR) of breast cancer and corresponding 95% confidence intervals (CI) according to dietary inflammatory index (DII) in the Iowa Women's Health Study, 1986-2011.

	DII Tertiles, HR (95% CI)			p_{trend}	DII continuous[d] HR (95% CI)
	< −2.08	−2.09 to −0.05	> −0.05		
Cases/Person years	950/ 213056	994/ 212780	990/ 211459		2934/ 637295
Model 1[b]	1 [a]	1.06 (0.97, 1.15)	1.09 (0.99, 1.20)	0.09	1.01 (0.99, 1.03)
Model 2[c]	1 [a]	1.07 (0.97, 1.17)	1.11 (1.00, 1.22)	0.06	1.01 (0.99, 1.04)

[a] Reference category.

[b] Age and energy adjusted

[c] Model 1 additionally adjusted for BMI, smoking status, pack-years of smoking, education, HRT use, oral contraceptive use, number of live births, education, age at menarche, age at menopause and history of hysterectomy.

[d] each point correspondss to a 1-unit increment in DII (corresponding to a 0.5 standard deviation increase)

Table 3

Hazards ratios (HR) of breast cancer and corresponding 95% confidence intervals (CI) according to tertiles of dietary inflammatory index (DII) within BMI subgroups, in the Iowa Women's Health Study, 1986-2011.

	Cases	DII Tertiles, HR (95% CI)[b]			*p* trend[c]	*P*interaction (DIIcontinous)	*P* interaction (DII tertiles)	DII continuous[d]
		< −2.08	−2.09 to −0.05	> −0.05		0.02	0.06	
BMI (kg/m^2)								
<25	1031	1 [a]	1.08 (0.93, 1.26)	1.06 (0.89, 1.25)	0.56			0.99 (0.96, 1.03)
25-30	1160	1 [a]	0.98 (0.85, 1.14)	1.04 (0.89, 1.22)	0.55			1.01 (0.98, 1.05)
>30	743	1 [a]	1.22 (1.01, 1.48)	1.35 (1.10, 1.66)	0.01			1.05 (1.01, 1.10)

[a] Reference category.

[b] adjusted for age, smoking status, pack-years of smoking, education, HRT use, oral contraceptive use, number of live births, education, age at menarche, age at menopause and history of hysterectomy and total energy intake.

[c] P-value for trend determined through linear method.

[d] Each point corresponding to a 1-unit increment in DII (corresponding to a 0.5 standard deviation increase)..